THE RELATION OF RENAL DISEASES TO DISEASES OF THE NERVOUS SYSTEM

BY

ROBERT T. EDES, M. D.,
OF WASHINGTON, D. C.

Read before the American Neurological Association at their Fourteenth Annual Meeting, held at Washingson, D.C., Sept. 18-19, 1888.

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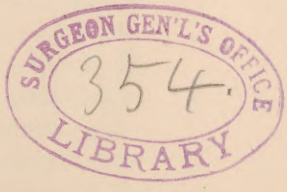

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THE RELATION OF RENAL DISEASES TO DISEASES OF THE NERVOUS SYSTEM.

BY ROBERT T. EDES, M. D.

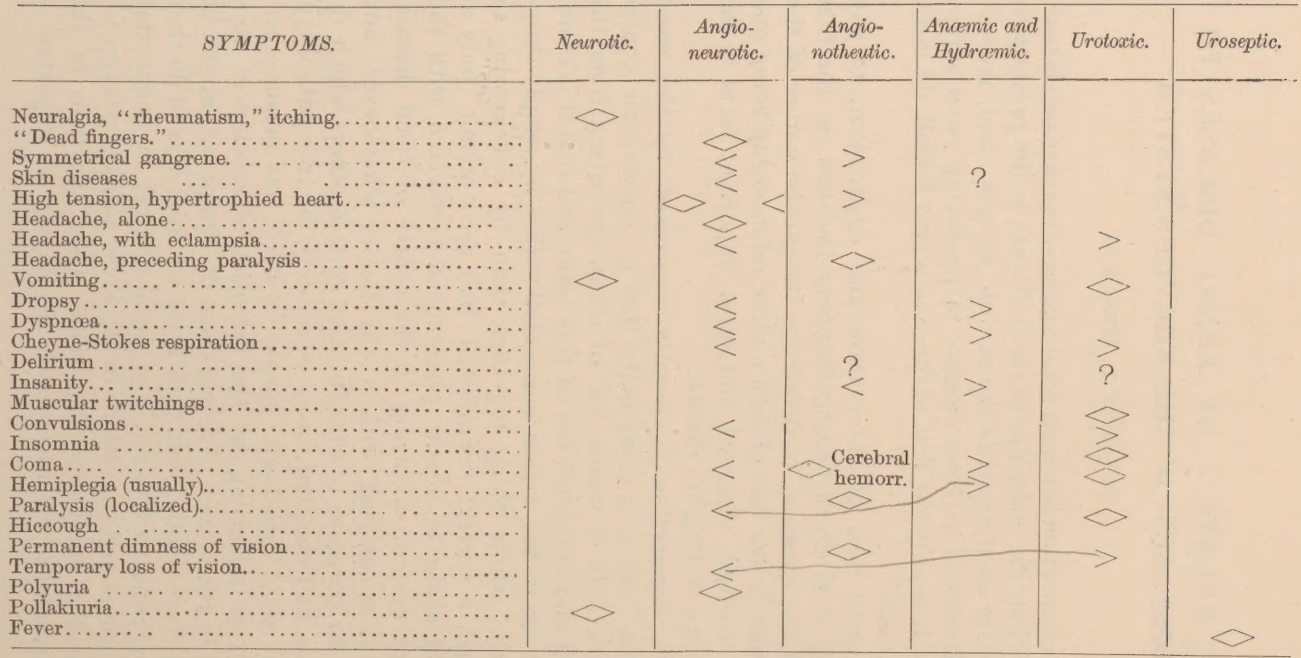
The connection between renal and nervous diseases is two-fold. First, the influence of renal disease in the production of diseases on the part of the nervous system; and, second, the influence of nervous diseases in producing renal symptoms. It is only the first of these to which I shall do more than allude.

A great deal of observation and experiment, to say nothing of much theorizing, has been lavished on the first part of the question, to determine the precise nature of the relationship; the fact of such a close relationship being one of the earliest observed and most important facts in the pathology of Bright's disease.

This connection is usually expressed by the word "uremia," and as it is my belief that a considerable confusion not only of words, but of ideas, has arisen from the general and undefined use of this term, and that it is easie to get rid of the errors connected with it by simply dropping the whole thing together, than by endeavoring to establish a correct definition, I shall use "uremic" only in the old sense to denote phenomena connected with the nervous system occurring in the course of renal disease, and not as carrying with it any theory whatsoever; and adopt for purposes of classification certain others which do express, as I consider, more accurately the true pathology.

The word "uro-toxic" speaks for itself, and means—pertaining to poisoning by the retention of substances contained in the urine. Another class of symptoms might be called "uro-septic," but with these we have less to do than the surgeons, to whom it is of great interest in connection with lesions and operations in the lower urinary passages.

For the symptoms dependent upon affections of the vessels, which are recognized as playing so important a



The closed parallelogram opposite any symptom and under any heading shows that the symptom may be wholly due to the cause signified. Half of the parallelogram shows that the cause noted at the head of the column is one factor.

part in the pathology of renal disease, the word "angiopathic" may be used, with the subdivisions "angio-neurotic" already in use, and "angio-notheutic," a word which I owe to the kindness and learning of my friend Dr. Fletcher, and which refers to symptoms or lesions dependent on organic disease or degeneration of the vessels (*αγγεῖον*, a vessel, *νόσος*, degeneration).

We find as symptoms accompanying acute and chronic diffuse nephritis in their various forms often enough to be legitimately recognized as having an intimate relationship therewith, and not being present merely as coincidences; convulsions, coma, delirium sometimes becoming insanity, headache, dyspnœa, failure of vision and hearing, paralyses, neuralgia, itching, sometimes cutaneous eruptions, "dead fingers," rarely symmetrical gangrene. These with vomiting, which is sometimes at least a nervous symptom, make the group known as uremic.

It is the object of this paper to insist upon the fact that they are not all urotoxic and to suggest the nature of the pathogenic connection.

The most obvious assumption, that which holds its own to the present day in some form and which does actually cover a part of the ground is, as the name suggests, that uremic symptoms are due to a retention in the blood of some excrementitious substance, whether water, urea, or some product of its decomposition, extractive, potash salts, or the totality of the urinary solids. Perhaps we may add to this list an alternative which seems to me to have a considerable degree of probability in its favor, but as yet little evidence, that new toxic agents perhaps in the nature of a ptomaines may be present in some cases. This might account for the difference between the great toleration of anuria from the arrest of the healthy secretion by mechanical means, and the rapid supervention of symptoms from a much less serious retention in chronic cases. This, however, is for the chemistry of the future to decide.

Such an accumulation of urinary solids is assumed to take place when the secretion becomes deficient in quantity, and it has been demonstrated by actual chemical

analysis in a certain number of cases, though as a matter of fact in much fewer than might be supposed from the frequency of the allusions, the water and the urea as being the larger part of the constituents are naturally those which have been most frequently examined. Data in regard to the others are too scanty to have great value.

It is not at all certain that urinary constituents are accumulating in all cases in which renal disease, even advanced, exists, and there can hardly be a better instance of the inconsistencies of medical reasoning than the indifference with which the removal of one kidney is spoken of in trust that the other will carry on the work of excretion thoroughly, and the promptness with which any symptoms that may arise in any stage of Bright's disease are attributed to a so-called uremia. A sort of reasoning in a circle takes place by which the pathological theory of uremia depending on an accumulation of urea is proved by the coincidence of these symptoms with known renal disease, and on the other hand, the diagnosis of renal disease is confirmed by the occurrence of symptoms supposed to depend upon the presence of urea in the blood.

A deficient secretion of urea or a secretion considerably less than that stated as a physiological average may undoubtedly take place in nephritis, even in the earlier stages; but it must be remembered that the thirty grammes per diem, which are often taken as the standard and which, as I have elsewhere[1] tried to show, are much too large an estimate for a considerable number of healthy persons, are not applicable to all persons, and certainly not to those whose digestion is imperfect, whose blood is deficient in red corpuscles, and who are undoubtedly making a much less than the proper amount of nitrogenous excreta. The quantity of urea varies from day to day both in health and disease, and a single observation cannot be properly regarded as conclusive of a diminished secretion. Unfortunately quantitative observations extending over several days are not so numerous as is desirable. Twenty grammes is probably a better aver-

[1] Read before Association of Physicians, 1888.

age for many persons, and low feeding and old age as well as many diseases which have nothing to do with the kidneys, may bring it much below.

The most convenient question with which to approach this inquiry is not: What are the nervous symptoms of Bright's disease? for this may refer either to the early stages, when the exact amount of secreting tissue thrown out of action is not known, but which may, in a great many cases, be fairly assumed to be much less than that removed by the ablation of one healthy kidney out of the pair, a loss which we know is perfectly well borne; or it may, and more frequently does, refer to the culmination of a long series of changes involving not only the kidneys, but heart, arteries, stomach, and blood, and perhaps organic changes in the nervous system itself.

A much simpler one, and one there is an abundance of clinical material to answer, is this, What are the symptoms of a total loss of function of both kidneys?

This is easy to answer. Cases of suppression of urine occurring in persons free from chronic diffuse nephritis, or where such a nephritis as bearing on only one kidney, has been unconnected with constitutional disease, have been recorded in considerable number, and in fact they present to us a series of pictures of as much uniformity as can be expected in clinical observation. It is interesting to notice, by the way, how strong is the influence of preconceived ideas, in the frequency with which authors introduce into their comments and into their titles remarks on the absence of the "usual" symptoms of uremia.

Dr. Roberts says: "When even the suppression is absolute, seven or eight days elapse before the special symptoms of uremic poisoning make their appearance; but when these do appear the end approaches rapidly, and death is not delayed beyond two or three days. Up to the rise of the proper uremic symptoms the condition of the patient is as a rule wonderfully calm and free from distress; the functions generally proceed tranquilly and the intelligence is undisturbed. The most distinctive and invariable of the special uremic signs are muscular twitchings. I believe

that these are never wanting. Contraction of the pupils is also a constant sign, but later in development than the muscular twitchings."

An examination of the cases collected by Dr. Fowler[1] and a number of later ones, although confirming the general accuracy of this description would lead to somewhat different conclusions in details.

The muscular twitchings, although occasionally mentioned, are not invariably so. They might, however, more easily escape observation than some other symptoms. The pupils are in some cases distinctly mentioned as dilated. Somnolence with restlessness, and, on the other hand, insomnia are very common. Convulsions are occasionally noted but they are by no means so common as one might expect from a comparison of these cases to Bright's disease, or in fact as the authors themselves seem to have expected. In the fatal cases death has come in two quite different ways. In one set the patient dies very quietly in the full possession of his faculties, and often a few hours or minutes after having been up, or engaged in conversation, *i. e.*, without any of the "usual" uremic symptoms. In the other, the end comes more in the usual way after an interval of the more classical sopor and coma.

Among the symptoms which have a special interest for our present inquiry, headache is sometimes, but not invariably, noted, not often spoken of as severe, and sometimes a sense of pressure in the head. Dyspnœa is noted in a certain but not large number.

We may describe these cases in general by saying that the poison of the urine is a slow one which produces but little disturbance for a number of days, *i.e.*, in small dose; and that a patient may recover after days of anuria, having hardly had an inconvenient symptom, or at a later period after those which are distinctly urotoxic.

When the blood has been thoroughly impregnated with the poison an effect upon the nervous centres is perceptible, which may go on to what is generally considered uremia, but which may produce death by an action on the

[1] Suppression of Urine, New York, 1881.

heart (and muscles of respiration?) before this condition has become at all prominent.

We may reckon as purely urotoxic symptoms: insomnia, restlessness, somnolence, mild delirium, sopor, and coma; muscular twitching, muscular weakness, rarely convulsions, sudden paralysis (of heart and respiratory muscles?); sometimes headache, sometimes dyspnœa, sometimes hiccough, frequently vomiting.

It is not necessary to our present inquiry to determine what is the special agent in the urine the accumulation which gives rise to these symptoms. Many theories, which I will not take up your time in detailing, have been framed and put to the test of experiment and clinical observation. The objections to assigning this place to urea were seen at an early day, and led to the making of the well-known ammonia theory of Frerichs with its supplements and modifications. Recent experiments have shown that large amounts of urea injected into the blood of animals deprived of the power of re-eliminating, produces symptoms comparable to uremia, and a proportion of urea somewhat approaching that which remains in the blood of these animals has been found in a few cases of uremia in man. It is possible that urea is the chief poison in these cases of suppression, but it is probable that it is at least assisted by the other normal constituents.

More recent observations attach importance to other constituents like extractive, and potash salts, but the most hopeful line of investigation at present lies in the investigation of self-formed poisons of greater subtlety and power.[1]

How far are these facts applicable to the symptomatology of chronic Bright's disease in any of its forms?

We meet with these phenomena, complicated with extreme anemia and debility, with œdema, not only of the subcutaneous tissue but of internal organs and with cardiac

[1] At the time this paper was read the author had not seen the suggestive but not quite conclusive work of Ch. Bouchard, "Sar les Auto-intoxications," Paris, 1887. This author assigns to urea little or no part in the total toxicity of the urine, much more to the potash salts, but concludes that there are several poisons in the urine not yet to be chemically defined. They are probably not alkaloids.

weakness, in the later course and at the end of chronic nephritis, and then there is no reason to find fault with their usual explanation as depending on a failure of the kidneys to do their work. They are then not only uremic in the ordinary sense, but truly urotoxic, and we see saturation of an enfeebled organism by a slowly administered poison, of which the last few, perhaps larger, doses bring the symptoms rapidly on.

There are cases, however, where these and other nervous symptoms are met with in the earlier periods of nephritis of either form before the renal disorganization has reached an extreme grade. In some the progress is undoubtedly toward atrophy with resulting uremia; in others the renal symptoms, though undoubtedly present and perhaps giving the name to the disease, are subordinated to the vascular and nervous ones.

So great may be the disproportion that Mahomed, whose early death was so great a loss to this department of pathology, used to speak of cases of "Bright's disease without nephritis," an error in nomenclature as it seems to me, since Bright's disease ought to be what Bright wrote about, which was undoubtedly the disease of the kidney, but yet indicating a view to which sufficient attention is not always paid.

In these the word "uremic" loses its usual or etymological signification, and is no longer synonymous with urotoxic. It is more by analogy than by actual demonstration that these symptoms are supposed to depend upon the same accumulation as takes place in the suppression we have been considering.

It is found in some of these that there is at the time of the outbreak a diminution in the amount of urine and of urea, but in many others more or less decided symptoms occur while the usual flow is going on or, at most, only some hours after it has become diminished.

This outbreak of symptoms very soon after the flow of urine has become diminished as regards the water, but where an increased specific gravity indicates that a considerable quantity of solid matter is still being carried off, is called uremic; and yet if the kidneys, which are still doing some work,

were removed entirely, as happened in the case of Dr. Polk (N. Y. Med. Journal, Feb. 17, 1883), or were entirely thrown out of action by any of the numerous accidents which may happen to the lower urinary passages, it would require eight or ten days for sufficient of the poison to accumulate to produce the symptoms.

It may be said that in such cases there has been, notwithstanding an abundant secretion of water, a retention of the solid elements of the secretion until they have accumulated to just on the brink of a poisonous dose which the temporary anuria causes them to exceed. Such a kind of retention seems possible when we consider the separate functions of the Malpighian bodies and the epithelium of the tubes, and, as regards any one constituent, it is difficult to disprove; but if we consider the water, the urea, and the total solids, we find that they may be excreted up to or even during the day of such an attack in a quantity which is not, to be sure, equal to the physiological average, but is not below what may be a fair quantity for persons with a much diminished tissue metabolism.

It may be remarked, as bearing on the probability of this form of retention usually taking place, that most of the substances found in the urine of which we have definite knowledge are diffusible, some of them highly so, and that in many cases of destruction of the kidneys by any of the various lesions of the lower urinary passages it is often remarked how small a quantity of renal tissue suffices to produce a large amount of water, and that in these cases uremic symptoms are deferred long after this destruction has been going on.

It is to be noticed also that the form of Bright's disease in which we hear most about its latency, where an outbreak of uremia occurs in the midst of apparent health, is not that in which the epithelium is the first to undergo degeneration, but the interstitial, where the vascular element is the predominant one.

In looking over a somewhat voluminous literature to find how close a correspondence exists between a diminished diuresis and an attack of well-marked uremia, it is

quite clear that in a large majority of cases either a gradual diminution in the amount of concentrated urine passed, or a somewhat slighter diminution with a low specific gravity, takes place when uremic symptoms are about to occur, and that the amount of water and solids not infrequently increases coincidently with the remission of the symptoms; but there are cases enough of an exceptional character to show that while we must regard the ordinary theory of the pathogenesis of the severer and more general symptoms of uremia, and, in particular, convulsions and coma without hemiplegia, as the correct one, yet there are cases to which it does not apply, and where we must seek, if not for an entirely different explanation, at least for another factor of great or controlling influence. In these cases are found chiefly headache, dyspnœa with Cheyne-Stokes respiration, coma with hemiplegia and unilateral convulsions, but also coma without hemiplegia, and general convulsions.

Bouvat (These de Lyon, 1883,) reports the case of a man of twenty-two with an acute nephritis, probably of scarlatinal origin, who had headache and eclampsia. The urine contained no albumen, but numerous granulo-fatty casts and much urate of sodium. During the time at which the attacks of eclampsia were taking place, there was no mention of the quantity of urine, but it was examined on every day and was not said to be scanty; two days after the last eclamptic attack, and while the patient was still somnolent, there were seventeen grammes of urea in two litres of water passed in the twenty-four hours. While the patient was still eclamptic there were found in the *blood* seventeen and nineteen centigrammes of urea per litre, an amount which the author thinks sufficient to prove the uremic character of the attacks, but which is so little in excess of the normal amount (ten centigrammes to the litre) and so insignificant in comparison with the amount which it is necessary to inject in order to produce decided symptoms in animals,[1] and which was found in some patients by Grehant and Quniquaud,[2] that the case seems to prove

[1] Six per cent. found in blood.

[2] Two to four per cent. found in blood. Comptes Rendus de l'Academie des Sciences, 1884, p. 383.

the contrary theory. It is interesting to note that delirium lasted for a week after the free discharge recorded had been going on.

Eiselt (Aertz. Ber. der K. K. Krankenhaus. Prag., 1884,) reports the case of a man who had well-marked nephritis and at one time maniacal attacks, supposed to be uremic, with other more usual symptoms. At a later period, after passing 1,200, 1,500 grammes of urine of sp. gr. 1,008 on two successive days, he had an epileptiform attack on the day on which the quantity rose to 2,840. On the next day it was 2,640, and he felt very well. On three days, at a subsequent period when passing 1,300 to 2,600, with sp. gr. of 1,006 to 1,016, he had vomiting and headache. Later the urine diminished in quantity, and he had eclampsia and somnolence under the usual circumstances, and the autopsy showed granular kidneys. Thomayer in commenting on this case speaks of other cases reported by B. Stricker and by Budde, in which uremic symptoms occurred with a daily amount of urine from one to two litres. The original reports of these I could not find.

The frequent occurrence of headaches, which are often so characteristic of interstitial nephritis for years before renal atrophy has advanced far enough to interfere with the secretion of a sufficient amount of urea, is well known.

The following cases show some of the relations of headache to urinary excretion.

C. H. W., æt. 40, commercial traveller. Headaches for a long time, growing worse and more frequent lately. Urine copious, with albumen and casts. Albuminuric retinitis, high arterial tension, severe headache and vomiting, relieved by morphia. Then left hemiplegia with relief of headache. From time to time until death, delirium, constant polyuria.

Solids in the urine as calculated from the total quantity and the specific gr., (which of course only gives a rough approximation),Sept. 21—87 grammes; Oct. 2—77; Oct. 13—51; Oct. 17—18; Nov. 1—100. At the time of the marked diminution of the middle of October it was noted that on October 10th he had morphia with relief of headache and

was more intelligent. The scantiness of urine lasted for about a week, during which he had no more severe headaches, but was slightly delirious, and the next mention of headache and restlessness occurs on October 30th, several days after the urine had again become abundant, and the day before one on which the calculation gives 100 grammes of solids. Does not this sequence seem much more like a fall and rise of tension than an accumulation of urinary solids?

The tracing of October 19th, during oliguria, but after the headache was relieved, shows a pulse of less than his usual tension, though no tracing was taken during the subsequent period of polyuria.

The patient died on December 13th, and the autopsy showed hypertrophy of the left ventricle with tracts of thickening here and there in the aorta. The kidneys were firm, granular, cystic and atrophied. The brain was unusually firm on section, with several small cyst-like cavities in the white and gray substance and spots of reddish-brown in various parts of the cortex and corpora striata. The arteries at the base had yellowish patches.

The diagnosis between Bright's with headache on the one hand, and cerebral disease with polyuria, no uncommon combination, on the other, is not always easy. Albumen and casts may be present in either. Localization of the headache, localization of any paralytic or spastic symptoms that may be present, study of the eye ground and of the heart and more than a single careful urinary examination may for a considerable time be all that can be depended on to make the distinction.

Headaches and polyuria are among the angio-neurotic phenomena which may belong to more than one disease, and it may be that they are not only not uremic, but, even when albumen and casts are present, not intimately connected with the local renal disease.

While recognizing the presence and importance of the uro-toxic origin of headache, I cannot believe this to be its usual one, considering the absence or rarity of headache in complete suppression of the urine, where it ought to be

present and to increase in intensity pari passu with the duration; and also considering its coming and going in ordinary cases in a way and under therapeutic influences more consistent with a neurosis than with any form of poisoning. If it be said that the relief which is afforded in some cases to the headaches of renal disease by the hot air bath is due to the elimination of the accumulated urinary products it may be answered that the bath relaxes the arterioles as well as carries off urea, and that the relief is often of too long duration to be explained simply by the removal of a certain excess of poison which must constantly be in process of renewal.

P. W., æt. 43, syphilitic ? headaches for two years. Queer feeling in head, left arm and leg. Convulsion and delirium. Urine; low sp. gr., albumen and casts, no retinitis. Fits repeated several times. Urine improved in character. Headache. Physical signs of consolidation and catarrh at apex of right lung. Gain in weight. Deep sleep, delirium and death.

Scalp thick, calvaria dense, thickening of dura, thickening of arteries at base, two tumors beneath the posterior part of the first temporal convolution on the right side. Left kidney small, but normal in structure to the naked eye. Right normal in size with slight depressions and adhesion of the capsule (chronic interstitial nephritis in incipient stages?) cavity in apex of right lung with cheesy contents (quiescent).

Miss J. P., very severe sick headaches with vomiting. Intervals of freedom. Albumen and casts in abundant urine, during intervals as well as during attacks. Mind clear till last day of life.

D. A., æt. 34. Headache, albuminuric retinitis, renal hemorrhage, albumen; granular, fatty, and blood casts; abundant urine, slight hypertrophy of heart; pain in back, copious renal hemorrhage soon followed by very severe headache, coma, and death. Probable cerebral hemorrhage.

Epilepsy may exist side by side with chronic nephritis, and a short observation would lead to either one of two

opinions, either of them erroneous, that the epilepsy produced sufficient congestion of the kidneys to cause casts and albumen, or that the fit was of a uremic character.

Thos. Fl., hospital repeater, æt. 40, epileptic as a child but not of late years until the present attack began, when he used to have one or two fits after drinking. He generally remained in the hospital a few days and was discharged "relieved" or "well." The urine always contained albumen casts, which became worse in character, and he died with chronic meningitis, hypertrophied heart, and interstitial nephritis.

The mental disturbances occurring in connection with renal disease have been discussed at some length, and spoken of as if some special relation existed between the two conditions. An attempt has even been made to give such a connection a medico-legal importance.

If we go back to our typical cases of retention, where we have the purest type of urinary poisoning, we find that many of them are distinguished by almost absolute mental clearness up to a very late period, and that in others a very mild delirium toward the last, and especially at night, is the utmost that can be observed in this direction.

It may be said with much confidence that insanity and delirium are not early, or distinctive, or common urotoxic symptoms.

At the termination of chronic Bright's disease, delirium is more common and more marked; but here we are dealing not only with retained secretion but with anemia, malnutrition, cardiac weakness, and other conditions which produce delirium in many other diseases.

An association with the peculiar nervous restlessness of interstitial nephritis is quite common.

In examining those cases, of which there is no inconsiderable number, where insanity in various forms, mania with excitement, lypemania with fixed delusions are present together with renal disease, it may be remarked, in the first place, that some of them do not bear a rigid scrutiny as cases of nephritis. In those where both affections are undoubtedly present, it is

true that in the later stages of the renal disease the urinary poisoning is one factor, but in others the insanity is too early a symptom to be attributed to urine poisoning. In one case given by Dieulafoy (Gaz. Hebd., 1845), where a man had attacks of hysterical violence, terrific hallucinations, lypemania, delirium of persecution, the urine was scanty but contained 39.9 per litre of urea. The patient recovered so far as his mental symptoms were concerned, and died two years later in coma without delirium.

A case reported by Raymond (Arch. Gen. de Med., 1882,) is of much interest as showing the relations of delirium to the excretion of urea.

A woman, æt. 66, had severe dyspnœa, with Cheyne-Stokes respiration, and entered the hospital on July 20th. On this day she passed 1,450 gr. of urine with 18.7 of urea in the twenty-four hours.

She continued to pass from 12 to 18 grammes every day until the 27th, when she began to be delirious.

There was then a period of three days in which no urine was passed (or none reported), and after this a much diminished secretion. It was not until nearly a month after the first diminution of urine that the patient became comatose.

As the patient was on an exclusive milk diet it is hardly to be supposed that with this amount of excretion there could have been an accumulation of urea at the time when the delirium began, though afterwards the increasing somnolence was probably due to gradual accumulation of the urinary poison.

The autopsy confirmed the diagnosis of chronic nephritis.

The connection is that of insanity with any severe depressing disease with a brain which may be disturbed by any one of several causes.

It may be perfectly proper to speak of the insanity of Bright's disease, or of "Folie Brightique," as a concise method of indicating the exciting cause, but not as denoting a special form of insanity.

Much interest has been recently awakened in a class, or two classes, of cases highly important in themselves and calculated to throw light on the pathology of so-called

uremia. I refer to those where symptoms that would naturally lead to a diagnosis of a localized cerebral lesion, such as hemorrhage or embolism, are shown, either by the rapidity with which they disappear or by an autopsy, not to be so caused; or where the suddenness and severity of an apoplectiform attack, especially but not exclusively in old people, lead to a similar diagnosis with a similar result. These are the "serous apoplexies" of a former generation and the uremia of latent Bright's disease of the present.

They are not, however, necessarily uremic even in the widest sense of the word, although it is true that a great many of them are. Still less are they urotoxic. From the character of the lesion they may occur in any disease with a feeble circulation and that condition of the vessels and blood which permits an easy and rapid escape of serum into the surrounding tissues; and as these conditions are frequently met with in advanced Bright's disease, it is not strange that the combination should be a common one.

In many of the cases reported the urine at the time of the accident has been found to be scanty, but it is by no means invariably the case that there is any evidence of a long accumulation, nor is the urine always *extremely* scanty, and as most of these cases occur in old persons where the normal amount of urea is considerably reduced (say to eight or ten grammes per diem), it is not at all certain that the full amount formed may not be secreted.

The great frequency of cerebral hemorrhage in interstitial nephritis, referrible to disease of the arterioles and to high vascular tension, is well known. A certain proportion of unilateral symptoms, and some general ones like coma, and perhaps rarely convulsions, are thus caused; and the headaches which precede them, as in a case already reported, are probably connected with the organic changes in the vessels, or with their condition of fullness rather than with any assumable excess of urea. To these cases, however, having an actual and well-defined lesion, it is very properly not usual to apply the word uremic even if they do accompany renal disease. It is understood that it is the vessel and not the blood which is at fault.

It is certainly repugnant to our notions that a poison gradually diffusing itself throughout the system should be supposed to affect only one side of the brain, and where we fail to find hemorrhage or closure of the vessels we naturally look for some other factor to determine the localization. In most of these cases a state of things is found to exist in the brain which has before been invoked to explain the general symptoms of uremia when the chemical theories have been deemed insufficient; but having been found not to exist in all cases, and thus being inadequate for a general theory, has been overlooked or regarded as of little importance. It is not so obvious as hemorrhage or softening, and may easily escape attention, especially when the tendency is to regard it as a common condition and not distinctive of anything in particular. This is œdema of the cerebral tissue with or without an increase of fluid in the ventricles. Such a condition may give rise either to no symptom at all or to the most serious ones, according to its degree, and the symptoms, when present, may be either generalized or local according as the lesion involves a large part of the cerebral centres or a limited area in the motor region.

One obvious objection to accepting this lesion as an efficient one, beside the fact that it is often present without symptoms, is that in the great majority of cases where hemiplegia has been present there has been no discernible difference in the two sides of the brain.

A slight difference in the degree of œdema between the two sides, or even more narrowly limited, would be very difficult to demonstrate, but might yet be sufficient to make the distinction between the paralysis of one side and the freedom of the other. It is certainly much easier to imagine this than a restriction of the action of a poison circulating in the blood to one side of the brain. Œdemas limited to a small area have been noted in other parts of the body. In a case of Dewevre (Lyon Med., 1886, p. 133), a patient who had "uremic" hemiplegia, had a few days previous a transitory, circumscribed œdema on the back of one hand.

In a few cases, however, a difference in the degree of œdema on the two sides has been noted, or a limited area

of well-marked anemia, or a difference of dilatation of the lateral ventricles. What should give rise to a greater degree of œdema upon one side than the other, it is impossible to say with certainty; but one who has watched the rapidity with which, especially in debilitated, emaciated, and flabby patients, the fluids of anasarca will seek the dependent parts, will have no difficulty in admitting the possibility that even so slight a circumstance as a person sleeping upon one side rather than the other might be enough to make the difference.

To illustrate the difference in symptoms which may come from a moderate inequality of pressure on one side when both sides are affected by the same lesion, I may mention the case of a man picked up unconscious, where coma and a well-marked hemiplegia led to a diagnosis of hemorrhage or softening, but where an autopsy showed that an acute meningitis of the convexity was the real lesion, the prominence of the paralytic symptoms on one side being accounted for by the greater thickness of the purulent layer upon the opposite surface of the cerebrum.

So it is not taking a long step in the dark to infer that the symptoms which, according to all physiological laws, ought to, and in the great majority of cases do, point to a focal lesion of some sort, do so in these cases as well, and that, as no other lesion is found, œdema is sufficient.

If we wish to ascertain, by an examination of the excretion, whether there is a more or less remote connection between urinary retention and the appearance of the symptoms, that is, whether, even if we cannot look upon them as directly urotoxic, they may not be indirectly so, we have by no means so many facts to guide us as might appear from the literature of the subject, already becoming voluminous in comparison with the length of time which has elapsed since it was considered that the presence of a distinct paralysis settled the diagnosis as against uremia. Most of the reports of these cases content themselves with a statement as to the presence or absence of albumen or sugar, which of course only implies that there was not absolute anuria. Even when a little more than this

is stated, it is curious to see how few physicians remember that to get a product you must have a multiplicand and a multiplier both. "Urea diminished" usually means percentage diminished, a statement of very little value alone.

Neither is the fact that at the moment of a paralytic or convulsive seizure the urine is scanty, any proof of an accumulation. As we have repeatedly had occasion to recall, it requires a week or more to fully develop purely urotoxic symptoms. Any severe shock or nervous affection may check for a time the flow of urine, and a few hours' suppression is much more likely to be the result than the cause of an apoplectic attack. In fact we know that alone it cannot be the cause in so short a time.

In the cases given by Raymond (Revue de Med., 1885), in not one have we the means of judging even approximately of the amount of urinary solids discharged. We can only say that there was not actual suppression, or near enough to it to excite remark. The cases of Chantemesse and Tenneson give no available data except that the urine is not expressly stated to be scanty, and in one case it had the specific gravity of 1017.

Florand and Canniot (Gaz. Med. de Paris, 1886, p. 532) report two cases, in the first of which the urine was dark and scanty; and in the other, where a hemiplegia lasted from the 4th to the 12th of October, with severe headache but no loss of consciousness, the urine was clear, not albuminous, and passed frequently in small quantities. In their remarks they use the expression "normal condition of urine." In this case there was no obvious focal lesion, but œdema of the brain and granular kidneys.

Buckling (Brit. Med. Jour., 1886, II. 1076) reports the case of a woman of 62 with hemiplegia of this kind, which recovered, and who passed an average of forty ounces a day with one per cent. of urea. This would give about twelve grammes of urea, a quantity below the assumed physiological average, but perhaps not below what we have a right to expect from a patient of that sex, age, and condition; nor approaching the condition of anuria, which, we must constantly repeat, takes a week at least to produce decisive results.

It is certainly a most unfounded assumption, in the face of the statements of the diminution of urea in old age, to suppose that all nervous symptoms in old persons not accounted for by some other obvious lesion are due to the senile kidney and consequent uremia. As is elsewhere remarked, there is no reason to suppose that the atrophy of the kidney is out of proportion to the diminished vital metamorphosis.

Hemiplegias without hemorrhage or softening are not confined to renal cases. An elderly colored woman, who had had for months swelling of the face, legs, and abdomen, with headache, dyspnœa, and palpitation, entered the Boston City Hospital with general anasarca of a passive kind affecting the hands and the dependent portions of the body. There was nothing decisive about the heart. The urine contained considerable albumen and casts, not of blood or waxy. The urea was noted as forty-one grammes per litre. A few days after she had a sudden hemiplegia without loss of consciousness.

The autopsy, made by an exceedingly careful pathologist, disclosed no plugging of the arteries or hemorrhage in the brain.

There was some dilatation of the heart, though the muscular substance was firm. The kidneys, though slightly reduced in size, showed no signs of nephritis, the diagnosis of the pathologist being "chronic cyanotic induration."

In some other cases reported it is very possible that the renal element may not be the controlling one, but rather a condition of cardiac failure and more or less localized vasomotor paralysis.

Level (These de Paris, 1888), who rejects the œdema theory, reports cases of this kind where nothing was found in the brain—one of these which seems to be of the kind where the exception proves the rule. A woman, æt 70, was brought into the hospital with complete resolution of the four limbs, conjugate deviation of the eyes to the right, and deviation of the labial commissure in the same direction. There was absolute insensibility of the left side.

Two days afterwards the paralysis had disappeared ex-

cept the deviation of the eyes, but the coma continued, and she soon died. There was atrophy of the kidneys depending on cancer of the uterus, and the consequent stoppage of the ureters. The heart was hypertrophied, but the brain was absolutely healthy, with very little atheroma of the arteries at the base. Such a case as this is open to any theory, but œdema, which may be local and transitory, can certainly be made applicable quite as easily as uremia which certainly is never local.

Certain experiments of Raymond, which show that a unilateral lesion, the obvious effects of which have disappeared, is sufficient to give a unilateral form to accidents due to urinary poisoning at a subsequent period are very interesting.

This hypothesis of a lesion which does not destroy the nervous elements, but is in fact compatible with a complete and rapid restoration of their function, or which may on the other hand so completely throw a large portion of the brain out of action as to cause rapid death, is not a new one in pathology. Besides its having always held a sort of reserve position in the present connection we are familiar enough with something like it in the so-called "congestive attacks" of coma or hemiplegia or excitement in the course of general paresis, or in the partial and often more or less transitory paralyses of cerebral syphilis attributable to a spasmodic action of arteries already narrowed by a specific endarteritis.

Œdema is well known to depend, if not always, at least often, upon a certain vaso-motor condition, a condition which may be present in the brain as well as in the subcutaneous cellular tissue, and it seems probable that we have in many of these nervous symptoms connected with renal disease the results of various vascular changes, ranging from spasm to paralysis acting as exciting causes upon a substratum of anemia, hydræmia, and cardiac debility, and perhaps often of contamination of the blood by retained urinary elements.

There are many other nervous symptoms which there is not time to treat in detail, especially as my object has

been not so much to describe them all as to comment on the erroneous pathology which groups them altogether as uremic. The "dead fingers" are so obviously a vaso-motor phenomenon that they speak of themselves against so comprehensive a classification. Amaurosis and some at least of the troubles of audition are probably referrible to the same causes as eclampsia. A very important nervous symptom, and one which is certainly at times a urotoxic phenomenon, is dyspnœa. This may arise in the course of Bright's disease from several causes, as œdema of the glottis or of the lungs. The one which concerns us is where none of these conditions is present. It is then very likely to be associated with Cheyne-Stokes respiration. Cuffer (These de Paris, 1878,) refers its causation to anemia and the diminished capacity of the tissues for oxygen.

In many cases of dyspnœa we find that the urine is diminished, but often it occurs when the urine is copious, very early in the disease, or at least early in the known course of the disease.

Uribe (These de Paris, 1886), gives a case from Rosenstein, where attacks of dyspnœa are noted at intervals, while the patient is passing an abundance of urine, as 5,000 of 1,008 sp. gr. and afterwards from 2,300 to 2,600 of sp. gr. 1,009 to 1,012. When intense dyspnœa was noted the amount was 500 grammes of sp. gr. 1,018. Still later when there was "extreme and continuous oppression" there was 1,500 of sp. gr. 1,015.

There was a certain amount of actual pulmonary lesion in this case, but the dyspnœa is evidently not attributed entirely to this by the reporter. There was hypertrophy of the heart and granular kidneys.

In a case of Hervier (These de Paris) the urine had always been normal in quantity, the mind was clear, and there was no œdema.

Fifteen days after beginning of the dyspnœa there was a sudden loss of consciousness with complete left hemiplegia. In some other of his cases the urine was diminished in quantity and deficient in urea.

Waldenburg reports the case of a man with uremic

asthma, headache and advanced renal disease. He improved under treatment, and did very well until he had a fit of passion, when the headache reappeared with vomiting and diminution of urine and tenderness on pressure in the region of the kidneys. There was relief from dry cups on the loins, but he began again to have dyspnœa, the urine being diminished one half. Digitalis gave relief, but did not much increase the diuresis, but the reporter states that, although the urine was much less than it had been, it was *about equal to that of a man in health.*

In a case of my own the patient's wife informed me that her husband, at a time when he was still going into town to attend to his business, used to hold his breath so long when asleep at night that she was frightened. I supposed this to be Cheyne-Stokes, which he afterwards manifested most distinctly. When he was dying in coma, and his face was encrusted with crystals of urea, the Cheyne-Stokes disappeared and the breathing was of the usual stertorous character. A brother of this patient, with interstitial nephritis, had the same symptom in the most typical form, but in his case it was among the terminal symptoms.

The case of Raymond, already quoted in connection with delirium, shows the coincidence of extreme dyspnœa with an amount of urea excretion fully equal to the formation.

The causation of the various nervous symptoms of renal disease (and the same may be said of many others which are beyond the limits of this discussion), is a complicated interaction of several causes, in one instance one condition and in another, another assuming the predominace.

For the sake of simplicity, we may speak of four principal factors:

1. Degeneration of the blood (anemia, hydremia, and perhaps other less understood conditions).

2. Poisoning of the blood (urea, potash salts, extractives, ptomaine ?).

3. Disordered vaso-motor action (spasm, paralysis).

4. Vascular degeneration (endarteritis, endophlebitis, fatty degeneration, miliary aneurisms).

Some of the earlier symptoms may be of a purely neurotic character.

In some cases mechanical obstruction or sudden paralytic or congestive anuria may bring the blood-poisoning to the front at once and without complication, but, with this exception, we are seldom in presence of so simple a state of things.

In chronic Bright's disease we are likely to find operative in the earlier stages those causes which have the least to do with marked organic changes. Angio-neurotic phenomena, and perhaps anemia, are in the foreground—the dead fingers, the headaches, the polyuria, and the asthma. As degeneration of the vessels progresses, we have hypertrophy of the heart, albuminuric retinitis, cerebral hemorrhage, and cerebral œdema; and when the kidneys fail to provide for the necessary excretion, the vomiting, convulsions, and coma, with a continuance of many of the former symptoms.

The action of certain drugs and therapeutic measures is very suggestive as to some of these points of pathology, as well as practically.

Ball and Jennings (L'Encephale, 1887, p. 295), in examining the state of the arterial tension in a case of chronic morphinism, find that during the period at which the effect of the dose has passed off and the demand for a new one is imperative, ["etat de besoin"] the sphygmograh gives the tracing of high tension which resembles, as is evident to any one familiar with this feature, the condition found in many cases of Bright's disease, and in fact considered by some persons as characteristic as the state of the urine. The comparison is expressly made by these authors. This indescribable condition of distress of the morphinist, which probably brings as much suffering bodily and mentally as anything short of severe and constant pain, is by no means dissimilar to the nervous restlessness often noticed in the patient with chronic interstitial nephritis, which probably has relations on the one hand with convulsions, and on the other with insanity.

Ball and Jennings find, as might be expected, that the

dose of morphine which brings the well-known comfort, reduces also the arterial tension to the normal point, but not only this, that some other drugs which stimulate the heart without raising or while reducing the tension also bring relief. These are sparteine and nitroglycerine. Is it not more probable that the great relief from many uremic symptoms by both well-known agents, morphine and nitroglycerine, should be much more closely connected with their action on the vascular tension than on any power which they might be supposed to have of assisting elimination, a power which there is not the slightest independent reason to attribute to them? So far as opium is concerned the effect is undoubtedly in the opposite direction.

These facts suggest a query which I propose to this society with a due sense of responsibility involved in an affirmative reply, and which I should hesitate much in putting before a less judicious body, namely, whether a physician would be justified not only in using morphine, as we all do, for the relief of nervous symptoms in the advanced stage of Bright's disease, but in instituting a treatment by small doses as soon as a diagnosis of chronic interstitial nephritis with high tension is established, using, of course, all measures to diminish as much as possible the injurious effects, in the way of diet, exercise and cathartics; or in other words making his patient a careful morphinist? We might go further and suggest the contrast between the calm of the satisfied opium eater and the restless worry and drive which I believe to be more than a coincidence in the middle aged business man who so frequently finds himself unexpectedly with Bright's disease in full force.

Copious diaphoresis by the hot air bath, or more recently under the influence of pilocartine is well known to be among the most efficient means of relief in uremic attacks, and the explanation usually given is that the urea or other urinary poison is carried off by the skin. It is true that a good deal of water is thus got rid of and a certain amount of urea and other solids accompany it; but no analysis has yet shown that all such supplementary outlets together cover the normal amount for the day, to say nothing of an accu-

mulation for a long time, such as is demanded by the retention theory. The same is true, so far as the solids are concerned, of the vomiting which carries off some solids ; and probably of the fecal discharges also. All these emunctories undoubtedly afford some relief, but the mere eliminative action cannot account for the more continued good effects which sometimes follow.

Such measures have, however, this in common with the drugs we have considered, that they relax a more or less extensive territory of arterioles, and diminish the general tension. Dry cups on the loins which carry off nothing are often useful in re-establishing diuresis. Bleeding, which can remove but a small fraction of the total urea in the body and which certainly cannot diminish the percentage in the blood, is of undoubted value in some cases of convulsions and has also been followed by prompt recovery in cases of cerebral œdema.